Permanent indwelling peritoneal catheters for palliation of refractory ascites in end-stage liver disease: a systematic review

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Permanent Indwelling Peritoneal Catheters for Palliation of Refractory Ascites in End-Stage Liver Disease: A Systematic Review

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Abbreviations

AE Adverse Events

AKI Acute Kidney Injury

ALFApump® (Automated Low Flow pump)

BP Bacterial Peritonitis

CDLQ Chronic Liver Disease Questionnaire

CLD Chronic Liver Disease

EoLC End of Life Care

ESLD End Stage Liver Disease

GA General Anaesthetic

HCC Hepatocellular Carcinoma

HDAS Healthcare Databases Advanced Search

HE Hepatic Encephalopathy

IQR Interquartile Range

LT Liver Transplantation

LVP Large Volume Paracentesis

MELD Model for End Stage Liver Disease

MeSH headings Medical Subject Headings

NICE National Institute for Health and Care Excellence

NIHR National Institute for Health Research

NOS Newcastle-Ottawa Scale

PD Peritoneal Dialysis

PIPC Permanent Indwelling Peritoneal Catheters

PRISMA Preferred Reporting Items for Systematic reviews and Meta-Analyses

QoL Quality of Life

RA Refractory Ascites

RCT Randomised Controlled Trial

SAE Serious Adverse Event

SBP Spontaneous Bacterial Peritonitis

TIPS Transjugular Intrahepatic Porto-systemic Shunt

tPA Tissue Plasminogen Activator

UK United Kingdom

Abstract

Background and aims

The incidence and mortality from end-stage liver disease is increasing, with a minority eligible for liver transplantation. Ascites is the commonest complication of end-stage liver disease and large volume paracentesis (LVP) the accepted management strategy where refractory to medical treatment. In malignant ascites, permanent indwelling peritoneal catheters (PIPC) are an established palliative intervention. The aims are to describe available data using permanent indwelling peritoneal catheters in refractory ascites due to end-stage liver disease.

Methods

Using systematic review methodology, databases were searched (MEDLINE, EMBASE, CINAHL [The Cumulative Index to Nursing and Allied Health Literature], Google Scholar and Cochrane Database of Systematic Reviews from inception-March 2018), for studies combining ascites and palliative care. Inclusion and exclusion criteria were applied to results.

Results

Following initial and updated searches, 225 studies were identified for full text review, 18 were eligible for final analysis. The studies displayed heterogeneity in design, reported on different indwelling catheters and were overall of low quality. Only one pilot randomised controlled trial was identified, of PIPC versus LVP, recruiting one patient into each arm. Technical insertion success was 100%, with low rates of non-infectious complications (<12%), none life

threatening. Rates of bacterial peritonitis were not unacceptably high (12.7%), considering this was an end-stage liver disease population and only a minority utilising long-term prophylactic antibiotics. Only one study attempted quality-of-life assessments; none addressed potential health economic benefits.

Conclusions

Despite lack of well-designed studies, preliminary data suggests low significant complication rates; however safety and efficacy of permanent indwelling peritoneal catheters in end-stage liver disease remains to be confirmed. Further prospective randomised controlled trials are warranted, potentially translating permanent indwelling peritoneal catheters into improved palliative care in end-stage liver disease.

Keywords

End Stage Liver Disease, Cirrhosis, Paracentesis, Ascites, Palliative care

Lay summary

The standard treatment for patients with advanced liver scarring (cirrhosis) and medically untreatable abdominal fluid (ascites) is repeated hospitalisation for drainage (large volume paracentesis, LVP). This article reports on the current available evidence of using long-term abdominal drains (PIPC) which remain permanently in the abdomen and reduce the need for repeated hospitalisation. We found low rates of serious complications. However, safety

and effectiveness of PIPC in people with cirrhosis needs to be confirmed by further research.

Introduction

In the UK over the last 40 years, the incidence of chronic liver disease (CLD) and related mortality has increased dramatically.[1] The complexity of palliative and end of life care (EoLC) in end-stage liver disease (ESLD) means the majority die in hospital,[2] with minimal specialist palliative care provided in hospice or community settings.[3]

Ascites develops in most (approximately 90%) with ESLD.[4–6] Refractory ascites (RA) either represents diuretic resistance (lack of response); or diuretic intolerance (development of complications precluding further use).[4,7] Upon developing RA, median survival is 6 months,[4] mandating liver transplantation (LT) consideration. Only a minority with ESLD (1.3%-12%)[8,5,9] undergo LT, due to ongoing substance misuse, alcohol recidivism, co-morbidity and in the context of a limited donor pool.[5,8–11] Additionally, such individuals are often also not deemed to be candidates for TIPS or the ALFApump® due to advanced disease stage.

Individuals with RA who are not LT candidates are therefore considered to be in a palliative phase, often dominated by the management of ascites as the commonest complication. The most accepted palliative intervention is large volume paracentesis (LVP), mandating repeated hospital attendance for insertion of a temporary drain.[4]

RA development has a major impact on quality of life (QoL) due to considerable symptom burden including abdominal distention, dyspnoea and poor appetite.[12] Frequent LVPs offer only limited relief as ascites re-accumulates.[12]

Permanent indwelling peritoneal catheters (PIPC) are an accepted strategy in the palliation of recurrent malignant ascites.[13,14] Two PIPC are commercially available, PleurX™ and Rocket® Medical.[14,15] A National Institute for Health and Care Excellence (NICE) technology appraisal reported low device-related infections (5.8%), 100% technical success and improvements in symptom control.[13]

There has been reluctance towards PIPC in ESLD due to concerns mainly regarding infection risk, specifically peritonitis.

Patients and methods

A search strategy was used, based on tables 4 and 5. The aim of this systematic review is to "identify and describe the current evidence available on the use of PIPC in RA due to ESLD". The PICOS structure (participants, interventions, comparators, outcomes, and study design) was used as described by PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses).[16]

Participants

RA in the context of ESLD.

Intervention

PIPC in the palliative management of RA.

Comparisons

Not relevant as no known comparison studies.

Outcomes

Including:

- Numbers of participants with ESLD
- Adverse events (AE) and complications, particularly infection related
- Use of prophylactic antibiotics
- Place of subsequent drainage
- Duration PIPC remained in situ
- Specialist palliative care support
- Participant survival following PIPC insertion
- Quality of life
- Health economics

Study design

Randomised controlled trials, prospective and retrospective cohort studies as well as case series were included.

Search strategy (see appendices)

A systematic electronic search was performed using: MEDLINE, EMBASE, CINAHL (The Cumulative Index to Nursing and Allied Health Literature), Google Scholar and the Cochrane Database of Systematic Reviews. Platforms used to access the databases were the Healthcare Databases Advanced Search (HDAS) and OVID. The initial search was undertaken in December 2015 (Table 1).

Table 1

The search themes related to ascites and palliative care, these were subsequently combined (Table 2). Search results were limited to English language. All levels of evidence were included due to paucity of available data.

MeSH headings and keyword search terms were constructed from pilot searches. References were exported into Endnote™ web basic reference manager.

Hand searching of reference lists in relevant manuscripts was performed. Online portals for major journals including Hepatology (American Association for the Study of Liver Diseases journal) and the Journal of Hepatology (The European Association for the Study of the Liver (EASL) journal) were searched for relevant publications and conference abstracts.

The search was updated on 13th March 2018 using the same methodology and search strategies. Articles were selected using the original exclusion and inclusion criteria (Table 3).

Table 2

Keywords and MeSH terms

Table 3

Eligibility criteria

Study selection

LM reviewed titles and abstracts of identified manuscripts for relevance and screened full texts applying exclusion criteria. AH independently reviewed a selection.

Quality assessment

The Newcastle-Ottawa Scale (NOS), developed to assess the quality of non-randomised studies including cohort studies, was used as a tool to assess those meeting inclusion criteria.[17]

Data extraction

LM designed a data extraction form which was applied to selected studies by LM and AH independently, with inconsistencies reviewed by SV.

Statistical analysis

Studies identified for full analysis were heterogeneous in design, therefore a descriptive approach was undertaken.

Results

The database search returned 11,043 results. A screen for duplicate results performed using Endnote™ resulted in 6634 being removed. A further 4230 were removed on the basis of: duplications not initially detected and exclusion criteria. Five full texts were unavailable from other UK libraries, however the titles met exclusion criteria. Full texts for the remaining 174 were reviewed. Citations were also identified through hand searching of journals, conference abstracts, reference lists of relevant manuscripts and those made known to the authors, yielding a further 51. In total, 225 studies were identified for full text review; 18 meeting full inclusion criteria for final analysis. (Figure 1)

Study characteristics

Of the final 18 studies included, one was planned as a pilot randomised controlled trial of PIPC versus LVP but only recruited one patient into each arm.[18] Three were prospective[19–21] and seven retrospective cohort studies;[22-28] one retrospective cohort study with matched controls;[29] five were case series[30-34] and one case report.[35] Of these, 12 studies were available as full manuscripts[18-21,23,24,26,28,29,32,34,35] and six as conference abstracts.[22,25,27,30,31,33]

Ten studies reported solely on RA due to cirrhosis;[18,21,22,24,27,30-32,34,35] of these, two were cohorts including both ascites and hepatic hydrothoracies.[22,27] These studies were not excluded due to the paucity of studies identified, though those with only hepatic hydrothoracies were excluded. The remaining eight studies described heterogeneous groups,[19,20,23,25,26,28,29,33] including ascites due to cirrhosis, malignancy and other aetiologies with one reporting on both abdominal and pleural indwelling catheters.[19]

Due to the small numbers identified, studies including both CLD and non-CLD aetiologies for ascites were not excluded. Studies without any participants with CLD as an aetiology were excluded.

Patient characteristics

Across all studies, 176 patients with refractory abdominal ascites due to cirrhosis were described. Separate studies independently reported on between one to 33 patients from this group. Cases of hepatic hydrothoracies which were described along with abdominal ascites,[22,27] have not been included in the final analyses.

Baseline liver disease severity scores were reported inconsistently; mean Model of End Stage Liver Disease (MELD) ranging from 10 to 22 and/or Child-Pugh B or C where reported.[20-22,24,25,27,28,29,32,34] The remaining eight studies did not report severity scores.[18,19,23,26,30,31,33,35]

Table 4 summarises the studies.

Table 4

Quality

The NOS, converting scores to the Agency for Healthcare Research and Quality standards of good, fair and poor;[17] rated 17 studies as 'poor', since none scored points in the comparison domain. The final study scored 8 as was a well designed pilot randomised controlled trial of tunnelled peritoneal dialysis catheters versus LVP, however it could not be rated higher than 'fair' due to only two patients being enrolled, one to each arm, the outcomes therefore being significantly limited.[18]

Type of indwelling catheter

All included studies reported on permanent indwelling devices; permanent indwelling (tunnelled) peritoneal catheters in twelve studies (both PleurX™ and Rocket®),[21-27,29-32,35] permanent subcutaneous port with intra-abdominal catheter (three studies)[19,20,34] and permanent tunnelled peritoneal dialysis catheters (three studies).[18,28,33]

Procedural insertion and success

There was a 100% technical success rate for insertion of catheters in ESLD; being inserted by interventional radiologists in eight studies,[19,20,22,23,26,27,31,34] six stating insertion was performed under ultrasound guidance.[19–21,23,26,34] Three studies stated drainage catheters were inserted with ultrasound guidance but not by whom.[21,24,35] Catheters were inserted by interventional nephrologists in two studies,[18,28] one stating under ultrasound and fluoroscopic guidance.[28] In a further two, catheters were inserted by consultant physicians/gastroenterologists under ultrasound guidance.[25,32] Two studies did not report on insertion methods;[21,30] one study reported catheters were inserted by trained physicians using X-ray guidance,[29] and one drainage

catheter was inserted surgically (Tenckhoff catheter)[33] (Table 4). There were no device related deaths.

Antibiotic prophylaxis

Nine studies used peri-procedural antibiotics for initial indwelling catheter insertion;[18–21,23,25,28,29,34] six of these did not use further ongoing long-term prophylactic antibiotics,[18-20,23,28,34] two used prophylaxis in limited cases.[21,29] Cephalosporins were used for peri-procedural prophylaxis in six studies,[19,20,23,25,29,34] with one using Metronidazole in addition,[19] two studies using peritoneal dialysis catheters used either Cefazolin or Vancomycin,[18,28] and a further solely using Sulbactam/Ampicillin.[21] In one study, two patients with cirrhosis were commenced on long term antibiotic prophylaxis following development and successful treatment of bacterial peritonitis (BP).[25] In these two cases,[25] drainage catheters were not removed but left in situ throughout. Four studies reported the use of long term antibiotic prophylaxis (Ciprofloxacin or Norfloxacin);[21,29,30,32] in one, a case series, prophylaxis was only used in the final two patients after review of the initial five cases,[32] a second used prophylaxis only if there was a history of prior spontaneous bacterial peritonitis (SBP) or according to EASL guidelines,[4,21] a third not defining in which population prophylactic antibiotics were used in.[29] The remaining thirteen studies did not report the use of long-term prophylactic antibiotics[18-20,22-24,26-28,31,33-35] (Table 4).

Place of management of ascites subsequent to device insertion

In nine of the 18 studies, subsequent ascites drainage was exclusively at home, either by community nurses, participants themselves or care givers.[18,21,23-25,28,31-33] Three reported ascites management in either a hospice

or participants' home;[19,30,35] in a further two, ascites management was either in a hospital outpatient setting, or the patients' home;[20,34] in one of these,[20] a small proportion (three of the total mixed cohort of 27) were also managed in hospital when admitted for unrelated medical conditions (Table 4). Four studies did not state the place of further ascites management (Table 4).[22,26,27,29] One study reported two patients required further hospital admission for full drainage with intravenous albumin cover. In none of the 14 studies which reported the place of subsequent drainage following PIPC insertion was hospital admission required for further ascites management.

Specialist palliative care

Of the 18 studies, 12 commented on PIPC performed as a palliative procedure (Table 4). [18-20,23,26,27,29-33,35] The remaining five used PIPC in both those who were and were not LT candidates.[21,22,24,25,34] Only three studies alluded to input from specialist palliative care services.[27,30,32]

Complications

Infectious and non-infectious complications in patients with ELSD are summarised in table 5.

Table 5.

Device related infections

All but two studies reported cases of bacterial peritonitis (BP) occurring in patients with ESLD,[26,29] however other infectious complications were not reported separately in this group. Complications, other than BP, have been described in those with ESLD where possible.

In six studies there were no episodes of BP in patients with ESLD.[19,23,28,32,33,35] In our case series we reported organisms (*Pseudomonas aeruginosa* and *Corynebacterium striatum*) cultured from the PIPC in one case,[32] however the clinical significance was uncertain. Nine studies reported cases of BP in ESLD,[20-22,24,25,27,30,31,34] of these, three defined BP, only two studies stated ascitic fluid samples were taken when clinically indicated,[27,34] rather than as routine. Two episodes of BP occurred despite norfloxacin prophylaxis.[21] Where PleurX™ PIPC were used in both abdominal ascites and hepatic hydrothoracies in ESLD, one case of BP was reported but not whether this was BP or bacterial empyema.[22] An additional case of *Escherichia coli* sepsis was reported, described as a "catheter related infection", without further information offered.[22]

In one study with the highest prevalence of positive ascitic cultures (42%, n=14),[24] further clarification sought from Reinglas et al confirmed that, in addition to sampling ascitic fluid in symptomatic patients, samples were also taken routinely throughout. It was unclear if these were taken from the PIPC or the abdomen. Organisms cultured were classified as typically associated with SBP in six (18%) and typically catheter-associated in 11 patients (33%).[24] Interpretation of routine ascitic fluid sampling in PIPC remains contentious, therefore it is unclear if all were true cases of BP.

Rates of BP varied from 0% to 42% across individual studies with an overall combined rate of 17% (29/166). Excluding the 11 patients in Reinglas et al with catheter related organisms,[24] the overall rate of BP was 12.7% (21 patients). If the Reinglas study was excluded as an outlier,[24] the overall rate of BP across the remaining 15 studies was 11% (15/133). Of these, four had the

PIPC removed and received antibiotics; eight were treated with antibiotics with PIPC left in situ; one was palliated as was end of life, in the remaining two, no subsequent management was described (Table 5).

Two studies with a mixed cohort of malignant and non-malignant ascites reported 11 cases of BP but without differentiating between aetiology.[26,29]

Cellulitis at catheter insertion site was reported in nine of 147 (6%) patients with ESLD.[21,24,27,32] Four mixed cohort studies reported 11 patients with either cellulitis or “local infection”; without stating underlying aetiology, therefore not included in analysis.[19,23,25,26]

Non-infectious complications

Of the 142 patients with ESLD and PIPC where complications were reported separately in this group; minor transient hyponatraemia and rise in creatinine was reported in 16 (11%) and 12 (8%) respectively,[21] leakage of ascites at exit sites 12 (8%),[20,24,30,34] catheter occlusion in eight (6%),[21,24,31,34] elevated serum urea in three (2%),[24] accidental catheter displacement in two (1%),[24,30] others 3% (n=4) (acute kidney injury (AKI) n=1, haematoma n=1, hepatic encephalopathy (HE) n=1 and blood stained ascites post insertion n=1).[20,24,32,34] (Table 5)

Two bleeding complications (haematoma and blood stained ascites following catheter insertion) were reported and both self-resolved.[24,34] Three with elevated serum urea were managed by reducing drainage episode frequency.[24] The AKI case followed leakage of ascites at an access port site.[20] The HE case had no clear precipitating cause, the authors felt likely representing ESLD progression.[32] This was the same case of *Pseudomonas aeruginosa* and *Corynebacterium striatum* grown from the PIPC with

uncertain clinical significance, without other features of infection or empirical antibiotics leading to improvement.[32]

In the eight studies with mixed RA aetiology, non-infectious complications were inconsistently reported in patients with cirrhosis, therefore included in table 5 where possible.[19,20,23,25,28,33] Complications without RA aetiology defined were; 13 cases of ascites leakage at catheter insertion site,[19,23,26] five unspecified catheter malfunctions,[23] five occluded catheters, three were peritoneal ports with patency restored after administration of tissue plasminogen activator (tPA);[19,26] four accidental catheter displacements,[25,26] two of groin pain,[26] one abdominal pain with BP excluded[25] and one port failure due to undiagnosed loculated ascites.[20]

Patient and PIPC survival post insertion

There was variable reporting of patient and PIPC survival, shown in table 4. Overall patient survival was limited, as expected in all aetiologies of RA. Where reported, median survival in ESLD varied between 29 days to six months,[25,32] consistent with known median survival in this group.[4] Median PIPC survival in ESLD ranged between six weeks to five months,[28,35] in-keeping with mean PleurX™ catheter survival in the malignant ascites NICE technology appraisal.[13]

Quality of life assessments

One study, Monsky,[19] described the impact of PIPC on QoL using a questionnaire similar to the Chronic Liver Disease Questionnaire (CDLQ).[36] Assessments were conducted following PIPC insertion; home care and hospice nurses were also surveyed. Patients reported improvements in

mobility and daily activities, however a pre-PIPC questionnaire was not recorded for comparison. Nursing staff stated PIPC benefited QoL and advocated earlier placement.[19]

No health economic assessments were undertaken.

Discussion

Main findings

The use of PIPC in the management of malignant ascites is well established.[13] In contrast, this is the first systematic review of PIPC in RA due to ESLD, summarising current international literature. It is not surprising that of the 18 studies identified, all but 12 were retrospective case series and/or cohort studies,[22-32,35] the one randomised controlled trial (RCT) identified was well designed, however only enrolled one patient into each arm.[18] Of the total 176 patients with ESLD and RA who underwent PIPC insertion, technical success was 100%, rates of non-infectious complications generally low (<12%) and none life threatening. Rates of the most feared complication i.e. BP (12.7%) were also not unacceptably high considering prophylactic long-term antibiotics were only used in 21/169 (12%) patients.[21,29,30,32,37] It is unclear if all reported cases of BP were true BP or due to colonisation, however these rates fall within that expected in ESLD (up to 14% in more recent data, 15%-19% in older data).[5,38] In patients undergoing peritoneal dialysis (PD), PD peritonitis is an accepted complication.[39] Current recommendations state rates should not exceed 0.5 episodes per year.[39] However, this cannot be extrapolated to PIPC in ESLD, this being a largely

palliative cohort focussing on symptom relief. This could explain why in some studies, development of BP did not mandate PIPC removal.[21,25,34]

Limitations

While the initial data on safety and efficacy of PIPC in ESLD and RA are encouraging, this needs to be interpreted with caution. Our systematic review describes PIPC outcomes in ESLD from heterogeneous, poor quality studies with small sample sizes, using a variety of different indwelling catheters, hence making direct comparison impossible. Data provided on the severity of liver disease (Child Pugh, MELD), patient and catheter related survival and prior history of spontaneous bacterial peritonitis (SBP) were limited and inconsistent. Prophylactic antibiotics were used in only three (12%) studies.[21,30,32] In the study addressing QoL, interpretation of results were hampered by suboptimal design.[19] Finally, none attempted to assess health economic outcomes of PIPC in ESLD and RA.

What this study adds

There is increasing burden from CLD deaths, representing the third commonest cause of premature death in the UK.[1] Most individuals with ESLD develop ascites which, in the absence of LT, is associated with a limited life expectancy.[4,6] Ascites causes physical and psychological symptoms, significantly impacting QoL.[4,12] The development of RA further limits prognosis, its management in the majority remains palliative, as only a small proportion are successfully transplanted.[4,10] LVP remains the commonest palliative intervention in RA, however offers limited symptom improvement,[12] necessitates repeated hospitalisations and can be associated with post-paracentesis circulatory dysfunction, HE, and rarely other complications.[40]

Further interventions for RA include invasive procedures such as peritoneovenous shunts, now virtually obsolete due to complications, the ALFApump® and TIPS.[4] Meta-analyses comparing TIPS with LVP reported TIPS to be more effective in reducing ascites recurrence, however with a greater incidence of HE (prevalence 15%-61%); with conflicting survival outcome data.[4] In one small retrospective study (n=10) of palliative TIPS for RA +/- hepatic hydrothorax in ESLD, 50% developed HE with more than half subsequently dying within three months.[41]

The ALFApump® involves an implantable device pumping ascites from the peritoneal cavity into the bladder.[42] Consistent with the initial European multicentre safety and efficacy study and the multicentre RCT,[43,44] recent studies have corroborated complication rates of infections (11%-56%),[45,46] renal dysfunction (21%-67%),[45-47] device deficiency including catheter occlusion (9%-33%)[45,46] and explantation rates of up to 30%.[46] Recent NICE guidance on the ALFApump® advises use only with 'special arrangements' and in research settings.[49]

TIPS and the ALFApump®, therefore, may be less appropriate as palliative interventions. Focus on interventional procedures may be at the expense of integrated holistic palliative care, symptom management and supporting discussions to establish future wishes.[48]

With an increasing burden from CLD and lack of effective palliative options for RA, the absence of data on PIPC is surprising.[10] PIPC are accepted management in recurrent malignant ascites, the NICE technology appraisal concluding PIPC clinically effective, having low complication rates, could improve QoL and were less costly than LVP.[13] A study using PleurX™ PIPC

in malignant ascites reported improvement in dyspnoea within two weeks of insertion.[50] Other potential benefits include patient autonomy and community-based care, allowing remaining life to be spent at their preferred place of residence.

Defining the final phase of illness in non-malignant life-limiting diseases can be challenging, though RA is a valuable prognostic guide in ESLD.[4] Despite this and the fact that the majority will be ineligible for LT, strategies for palliative management in ESLD are not well defined or integrated.[5,9,10] As complex EoLC needs are often present, management remains mainly within secondary care with over 70% dying in hospital.[2,51] In England, despite pockets of excellence,[52] little specialist palliative care is provided in hospices or the community, despite services being available.[2,3]

Only a small proportion (7.5%) of patients with cirrhosis receive an out-patient palliative care consultation despite symptoms or disease severity; the only predictor of palliative care referral being concomitant hepatocellular carcinoma (HCC).[53] An early palliative care intervention in patients referred for LT assessment reported 50% of moderate to severe symptoms significantly improved.[54]

Local data in those with RA undergoing LVP showed that only 33% overall were referred to specialist palliative care despite a minority, 12%, being listed for LT.[9] A survey amongst UK consultants suggested potential contributors being inadequate understanding of the fluctuating disease trajectory and discomfort with the subject of palliative care in ESLD.[55]

There have been calls to improve the quality of care for those living with and dying from ESLD with greater and timelier integration of palliative care.[3] This

and the initial positive experiences of PIPC, prompted our group to obtain National Institute for Health Research (NIHR) funding for a prospective feasibility RCT comparing palliative PIPC (Rocket®) with LVP in ESLD (REDUCe Study, ISRCTN 30697116).[56] This mixed methods study has collected clinical, qualitative, patient reported and health economic data to inform a potential future definitive RCT.[56] Initial results are encouraging.[57] Although being a UK based trial, the implications could be international, the ultimate aim being to improve EoLC and contribute to the understanding of palliative care needs of those with RA due to ESLD.

Conclusions

This systematic review has described the use and preliminary safety and efficacy data of PIPC in RA and ESLD, with only two further hospitalisations for ascites drainage required. Though the prevalence of peritonitis was no higher than that seen in an ESLD population, the lack of well-designed studies impacts the pooled analysis. This underlines the need for well-designed RCT to assess the safety and efficacy of PIPC in RA in ESLD, aiming to improve QoL. This will contribute to a growing body of international evidence to support those with ESLD and RA in receiving more equitable palliative and EoLC care as in other non-malignant life-limiting diseases.

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Tables

Databases	Date initial search performed	Date repeat search performed
Medline (HDAS) (1946 to date of search)	7.12.15	13.03.18
Medline (OVID) (1946 to date of search)	3.12.15	13.03.18
Embase (HDAS) (1974 to date of search)	4.12.15	13.03.18
Embase (OVID) (1974 to date of search)	7.12.15	13.03.18
CINAHL (HDAS) (1981 to date of search)	8.12.15	13.03.18
Cochrane Database of Systematic Reviews	8.12.15	13.03.18

Table 1 Databases used in search

Keywords

Ascit*, “refractory ascit*”, “resistant ascit*”, (refractory AND ascit*), (resistant AND ascit*), “ascitic drain*” (ascitic AND drain*), “diuretic intolerant ascit*”, paracentesis, “palliative medicine”, palliat*, “terminal care”, terminal*, “palliative care”, (palliative AND medicine), (palliative AND care), (terminal AND care), “end of life care”, (end AND of AND life AND care), (hospice AND care), hospice*.

MeSH Terms

ASCITES, ASCITIC FLUID, PORTAL HYPERTENSION, TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT, PARACENTESIS, TERMINAL CARE, TERMINALLY ILL, PALLIATIVE CARE, PALLIATIVE MEDICINE, HOSPICE AND PALLIATIVE CARE NURSING, HOSPICE CARE, HOSPICES

Table 2 Keywords and MeSH Terms

Inclusion criteria	Exclusion criteria
Adult participants (≥18 years of age)	Paediatric participants (<18 years of age)
PIPC for recurrent drainage of ascites secondary to liver disease	Animal studies
English language articles	Shunting devices (including peritoneovenous, TIPS) and ALFApump®
	Manuscripts reporting solely on malignant ascites and/or patients undergoing chemotherapy

Table 3 Inclusion and exclusion criteria

Author, year (country), Design	Population and drainage site/ Number of cases with cirrhosis related ascites	Type of PIPC/ Place of insertion	Prophylactic antibiotics	Palliative or non-palliative	Place of further ascites management	Patient survival post PIPC insertion/ Duration PIPC remained in situ
Ahmed, 2018[18] (Canada) Prospective pilot single centre randomised controlled trial project report	Cirrhosis; Peritoneal n=1 (1 patient in peritoneal dialysis catheter arm, 1 in standard care arm)	Tunnelled peritoneal dialysis catheters Interventional nephrologist	During insertion procedure only - Cefazolin or Vancomycin	Non-LT candidates; Palliative care not mentioned	Home (self-drainage by patient)	Reported the patient completed study follow up period of 6 months/ Not reported
Corrigan et al, 2018[27] (UK) Retrospective cohort study (Conference poster)	Cirrhosis; Peritoneal and pleural n=24 (total 29 catheters in 28 patients with ascites and hepatic hydrothorax – not distinguished in abstract)	Unspecified tunnelled indwelling peritoneal catheter Interventional radiologists	None	Non-LT candidates 24 patients referred to palliative care	Not stated	6 and 12 month survival available on 24 patients; 50% and 25% respectively/ Not reported
Hingwala et al, 2017[28] (Canada) Retrospective cohort study	Mixed; Peritoneal n=8	Tunnelled peritoneal dialysis catheters Interventional nephrologist under ultrasound and fluoroscopic guidance	During insertion procedure only - Cefazolin or Vancomycin	Not stated	Home (self-drainage by patient	Median catheter survival 146 days (interquartile range 33.5-1039 days)

Author, year (country), Design	Population and drainage site/ Number of cases with cirrhosis related ascites	Type of PIPC/ Place of insertion	Prophylactic antibiotics	Palliative or non-palliative	Place of further ascites management	Patient survival post PIPC insertion/ Duration PIPC remained in situ
Imler et al, 2012[22] (USA) Retrospective cohort study (Conference poster)	Cirrhosis; Peritoneal and pleural n=16 (26 total ascites and hepatic hydrothorax)	PleurX™ Interventional radiology database (insertion method not mentioned)	None	Patients on LT list as well as palliative. No mention of palliative care	Not stated	30 and 90 day mortality after device insertion: 30.8% and 61.5% respectively/ Not reported
Knight et al, 2017[26] (USA) Retrospective cohort study	Mixed; Peritoneal n=3	PleurX™ Interventional radiologists - ultrasound guidance	None	Palliative intent but no specific palliative care input mentioned	Not stated however stated no concomitant LVP required	Median survival from insertion to death 85 days
Kriese et al, 2013[30] (UK) Retrospective case series (Conference poster)	Cirrhosis; Peritoneal n=4	PleurX™ Not stated	Ciprofloxacin	Palliative intent but no specific palliative care input mentioned	Home/ hospice	Not reported/ Catheter in situ for a median of 30 days (20 – 50) before removal or death
Kundu et al, 2012[31] (USA) Retrospective case series (Conference poster)	Cirrhosis; Peritoneal n=12	Unspecified tunnelled indwelling peritoneal catheter Interventional radiologists	None	Non-LT candidates; Palliative care not mentioned	Home (self-drainage by patient)	Not reported/ Median duration of catheter function 2 months

Author, year (country), Design	Population and drainage site/ Number of cases with cirrhosis related ascites	Type of PIPC/ Place of insertion	Prophylactic antibiotics	Palliative or non-palliative	Place of further ascites management	Patient survival post PIPC insertion/ Duration PIPC remained in situ
Lungren et al, 2013[23] (USA) Retrospective cohort study	Mixed; Peritoneal n=7	PleurX™ Interventional radiologists - ultrasound guidance	During insertion procedure only - Cefazolin or Clinamycin	No mention of palliative care other than some overall discharged to USA hospice care*	Home – patients or carers/hospice	Not reported/ Mean catheter survival 60 days (0-796 days), (11,903 cumulative catheter days)
Macken et al, 2016[32] (UK) Retrospective case series	Cirrhosis; Peritoneal n=7	Rocket® Ultrasound guidance, (gastroenterology) physicians	Ciprofloxacin/ Norfloxacin after review of first 5 cases	Non-LT candidates, reviewed by palliative care team	Home (district nurse)	Median patient survival 29 days (8-219)/ Not reported
Monsky et al, 2009[19] (USA) Prospective cohort study with QoL assessment	Mixed; Peritoneal and pleural n=2 (further 1 with hepatic hydrothorax)	Peritoneal and pleural catheters with percutaneous access ports (Celsite DRAINAPORT) Interventional radiologists – ultrasound and fluoroscopic guidance	During insertion procedure only - Cefazolin and Metronidazole	No mention palliative care except USA hospice care*	Hospice/ home care nurses	Not reported/ Not reported

Author, year (country), Design	Population and drainage site/ Number of cases with cirrhosis related ascites	Type of PIPC/ Place of insertion	Prophylactic antibiotics	Palliative or non-palliative	Place of further ascites management	Patient survival post PIPC insertion/ Duration PIPC remained in situ
Po et al, 1996[33] (USA) Prospective case series (Conference poster)	Mixed; Peritoneal n=1	Peritoneal dialysis (Tenckhoff) catheter Surgical insertion	None	No mention palliative care input. "Terminally ill patients" suggests palliative intervention	Home, by patient	Mean duration of survival 6 months/ Not reported
Reinglas et al, 2016[24] (Canada) Retrospective cohort study	Cirrhosis; Peritoneal n=33	PleurX™ Tunnelled indwelling peritoneal catheter Ultrasound guidance. Not stated by whom	None	LT candidates and non-LT candidates Described as palliative management but not palliative care input	Home care nurses	Not reported/ Median duration 117.5 days
Reisfield et al, 2003[35] (USA) Case report (total of 5 cases)	Cirrhosis; Peritoneal n=5	PleurX™ Tunnelled indwelling peritoneal catheter Ultrasound guidance, not stated by whom	None	Non-LT candidates. USA hospice care* mentioned but not integrated palliative care	Hospice then at home, initially by hospice nurse then by patient and family member	Mean duration of catheters in situ was more than 6 weeks – all remained in situ until the time of death/ Mean duration more than 6 weeks

Author, year (country), Design	Population and drainage site/ Number of cases with cirrhosis related ascites	Type of PIPC/ Place of insertion	Prophylactic antibiotics	Palliative or non-palliative	Place of further ascites management	Patient survival post PIPC insertion/ Duration PIPC remained in situ
Riedel et al, 2018[29] (Denmark) Retrospective cohort study with matched cohorts	Mixed; Peritoneal n=7	PleurX™ Tunnelled indwelling peritoneal catheter Trained physicians, x-ray guided	Cefuroxime during insertion procedure Reported 16 patients received further prophylactic Ciprofloxacin but not which cohort	Non-LT candidates; Palliative care not mentioned	Not stated	Mean survival 200 days
Rosenblum et al, 2001[34] (USA) Prospective case series	Cirrhosis; Peritoneal n=9	Peritoneal catheter with access port (modified venous access ports) Interventional radiologists under ultrasound and fluoroscopic guidance	During insertion procedure only - Cefazolin	LT candidates and supportive care. No mention of palliative care input	Nurse in gastroenterology outpatient clinic and 2 in community by visiting nurse	Not reported/ Mean port patency was at least 255 days with a total of 1557 port days

Author, year (country), Design	Population and drainage site/ Number of cases with cirrhosis related ascites	Type of PIPC/ Place of insertion	Prophylactic antibiotics	Palliative or non-palliative	Place of further ascites management	Patient survival post PIPC insertion/ Duration PIPC remained in situ
Savin et al, 2005[20] (USA) Prospective cohort study	Mixed; Peritoneal n=4	Peritoneal catheter with access port (Port-a-cath peritoneal implantable access system) Interventional radiologists under ultrasound and fluoroscopic guidance	During insertion procedure only - Cefazolin	Palliative management. Palliative care input not mentioned	Hospital outpatients and as inpatient, as well as at home with visiting nurses	Not reported/ 1810 port days (in 27 patients in the total mixed cohort)
Semadeni et al, 2015[25] (Switzerland) Retrospective cohort study (Conference poster)	Mixed; Peritoneal n=9	PleurX™ Tunnelled indwelling peritoneal catheter Gastroenterology consultant under ultrasound guidance	During insertion procedure - Ceftriaxone. Two cases received prophylaxis with Norfloxacin and Ciprofloxacin, respectively after developed and treated for BP	LT candidates and non-LT candidates Palliative care not mentioned	Home (by patient)	Mean survival in patients with cirrhosis 192 days/ Mean catheter survival in patients with cirrhosis 111 days

Author, year (country), Design	Population and drainage site/ Number of cases with cirrhosis related ascites	Type of PIPC/ Place of insertion	Prophylactic antibiotics	Palliative or non-palliative	Place of further ascites management	Patient survival post PIPC insertion/ Duration PIPC remained in situ
Solbach et al, 2017[21] (Germany) Prospective cohort study	Cirrhosis; Peritoneal n=24	PleurX™ Tunnelled indwelling peritoneal catheter Ultrasound guidance. Not stated by whom	During insertion procedure Sulbactam/ Ampicillin. Norfloxacin 15/24 63% - in prior history of SBP and defined risk factors as per EASL guidelines	LT candidates and non-LT candidates Palliative care not mentioned	Home (by patient)	16/24 67% remained in situ until death (mean 97.6+/- 51.4 days). Five patients listed and underwent LT/ Mean indwelling catheter time 83.2+/- 54.3 days

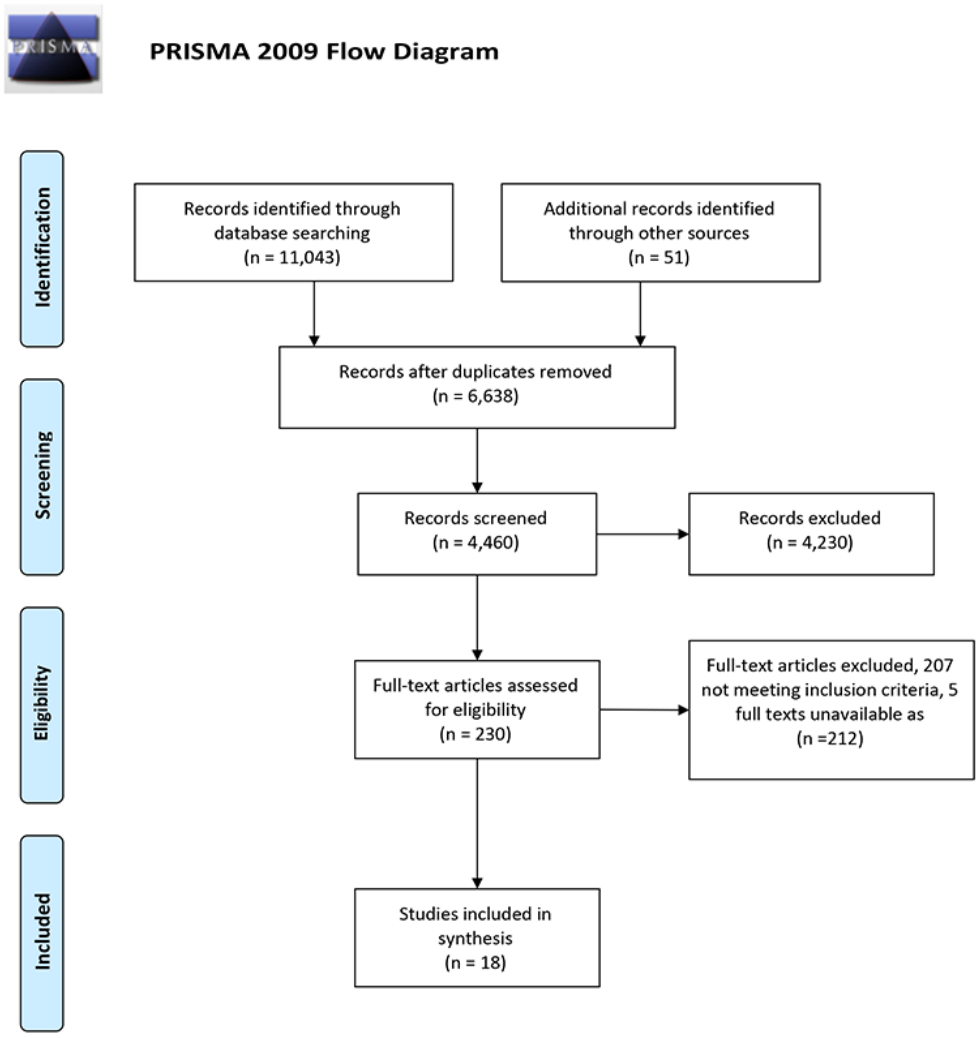
Table 4 Summary of studies included in the systematic review
USA = United States of America, UK = United Kingdom, Mixed = malignant and cirrhotic ascites as well as ascites due to other causes, QoL = quality of life, LT = liver transplant, LVP = large volume paracentesis, BP = bacterial peritonitis, SBP = spontaneous bacterial peritonitis. *It is worth noting that in the USA that phrase “Hospice care” is usually interpreted as only being instituted late in disease (on average 14 days before death for all diseases). This differs from UK interpretation where “Hospice care” can be instituted synchronously with active/secondary care.

Author, year (country), Number of cases (n)	Bacterial peritonitis	Cellulitis	Non-infectious complications
Ahmed 2018[18] (Canada) n=1	Not reported	Not reported	Not reported
Corrigan et al, 2018[27] (UK) n=24	3 (12.5%) received antibiotics after admission with abdominal pain, 2 having positive ascitic taps	3 (11%) with skin site erythema and positive skin swabs – not reported if received antibiotics Not reported if occurred in abdominal or pleural drains	3 leaking insertion sites (not reported if pleural or abdominal) 1 catheter blocked and subsequently removed
Hingwala et al, 2017[28] (Canada) n=8	None	None	None
Imler et al, 2012[22] (USA) n=16	1 (6%) – not specified if BP or spontaneous bacterial empyema	None	None
Kriese et al, 2013[30] (UK) n=4	1 (25%), non-fatal, catheter removed and replaced	None	1 (25%)accidental removal of catheter, 1 (25%) leakage of ascites at insertion site (same as patient as developed BP)
Kundu et al, 2012[31] (USA) n=12	2 (17%), catheters removed, treated with antibiotics	None	1 (8%) obstructed drain, re-sited
Lungren et al, 2013[23] (USA) n=7	None	3 (but included patients with mixed aetiology for RA and aetiology not specified)	5 “catheter malfunction” unspecified, 4 ascites leakage at incisional site (requiring suture placement) (but included patients with mixed aetiology for RA and aetiology not specified)
Macken et al, 2016[32] (UK) n=7	None	2 (29%) one treated with antibiotics, one drain removed and re-sited after treatment	HE of unclear cause

Author, year (country), Number of cases (n)	Bacterial peritonitis	Cellulitis	Non-infectious complications
Monsky et al, 2009[19] (USA) n=2	None	3 (but included patients with mixed aetiology for RA and aetiology not specified)	3 temporary occlusions (patency restored using tPA infusion), 3 self-limiting ecchymosis, 1 leakage of ascites (but included patients with mixed aetiology for RA and aetiology not specified)
Po et al, 1996[33] (USA) n=1	None	None – none reported in mixed cohort	None – none reported in mixed cohort
Reinglas et al, 2016[24] (Canada) n=33	14 (42%) with positive routine peritoneal fluid cultures; 6 with typical SBP organisms 6 catheters removed, all patients successfully treated with antibiotics	3 treated with antibiotics – no mention if catheter removed	7 (21%) ascites leakage at PIPC site – 5 resolved, 1 PIPC removed, 1 further sutures around PIPC, 1 eventual PIPC removal due to persistent leakage. 3 (9%) rise in urea 3 (9%) PIPC occlusions (1 patency restored using tPA, 2 successful PIPC replacement) 1 (3%)accidental catheter displacement 1 (3%) haematoma, resolved
Reisfield et al, 2003[35] (USA) n=5	None	None	None
Rosenblum et al, 2001[34] (USA) n=9	3 (33%), 1 treated with intravenous antibiotics, 1 port removed, 1 palliated (no active treatment)	None	3 (33%) ascites leakage at PIPC site - patient subsequently developed BP 1 (11%) PIPC occlusion 1 (11%) blood stained ascites

Author, year (country), Number of cases (n)	Bacterial peritonitis	Cellulitis	Non-infectious complications
Savin et al, 2005[20] (USA) n=4	1 (25%), management not reported mixed cohort but specified as being in ESLD patient	None – none reported in mixed cohort	1 (4% of total mixed cohort) leakage at site - in ESLD patient - same patient who developed BP 1 (4% of total mixed cohort) AKI – specified as being in ESLD patient 1 (4% of total mixed cohort) loculated ascites recognised after PIPC insertion
Semadeni et al, 2015[25] (Switzerland) n=9	2 (22%), treated with antibiotics, catheters remained in situ, subsequently started prophylactic antibiotics	2 “local infection” (but included patients with mixed aetiology for RA and aetiology not specified)	2 (4% of total mixed cohort) accidental catheter dislocation 1 intermittent abdominal pain with BP excluded (but included patients with mixed aetiology for RA and aetiology not specified)
Solbach et al, 2017[21] (Germany) n=24	2 (8%), treated successfully with antibiotics Developed despite Norfloxacin prophylaxis	1 (4%) – same patient developed BP	16 (67%) minor transient hyponatraemia at week 4 12 (50%) small transient increase in creatinine at week 12 2 (13%) PIPC occlusion – resolved with flushing 1 (4%) complete PIPC occlusion – further PIPC re-sited 1 abdominal pain with BP excluded – resolved with placement of shorter catheter

Table 5 Infectious and non-infectious complications in patients with ESLD and PIPC
USA = United States of America, UK = United Kingdom, Mixed = malignant and cirrhotic ascites as well as ascites due to other causes, QoL = quality of life, SBP = spontaneous bacterial peritonitis, AKI = acute kidney injury, tPA = Tissue plasminogen activator



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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